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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,288	06/08/2000	Guo-Liang Yu	PF343P3C5	1519

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/03/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/589,288	YU ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-91,118-124 and 148-180* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-91,118-124 and 148-180* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Status of Application, Amendments and/or Claims

The amendment of 12 February 2003 (Paper No. 15) has been entered in full. Claims 124, 148, and 158 are amended and claims 181-182 are cancelled.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 85-91, 118-124, and 148-180 are under consideration in the instant application.

Specification

1. The disclosure is objected to because of the following informalities:

2. The Brief Description of Drawings for Figures 4A-4C at pg 15 of the specification do not make reference to the SEQ ID NO of "HNEDU15X".

3. Patent applications are referenced throughout the disclosure (for example pg 433, lines 12-14). The status of the applications must be updated.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. Claims 85-91, 118-124, and 148-180 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis

for this rejection is set forth at pg 2-6 of the previous Office Action (Paper No. 13, 13 August 2002).

The claims are directed to a method of treating an autoimmune system disease or disorder, rheumatoid arthritis, or systemic lupus comprising administering to an individual a therapeutically effective amount of an antagonistic antibody or portion thereof that specifically binds a protein consisting of an amino acid sequence of residues 134-285 of SEQ ID NO: 2. The claims also recite a method of inhibiting lymphocyte proliferation, differentiation, or survival by administering various fragments of the amino acid of SEQ ID NO: 2. The claims recite a method of inhibiting lymphocyte proliferation, differentiation, or survival comprising administering to an individual a therapeutically effective amount of an antagonistic antibody or portion thereof that specifically binds a protein consisting of an amino acid sequence of residues 134-285 of SEQ ID NO: 2. Finally, the claims are directed to a method of treating an autoimmune disease or disorder or rheumatoid arthritis comprising administering to an individual a therapeutically effective amount of an antagonistic antibody that specifically binds an isolated neutrokine-α protein purified from a cell culture wherein said cell culture comprise a polynucleotide encoding amino acids 1-285 of SEQ ID NO: 2.

Applicant's arguments (Paper No. 15, 12 February 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that Example 7 of the specification provides a working example for stimulation of B cell proliferation and differentiation. Applicant argues that working examples are not required to satisfy the enablement criteria of 35 U.S.C. § 112, first paragraph. Applicant contends that the specification discloses that neutrokine-alpha promotes lymphocyte

proliferation, differentiation, and survival (paragraphs [0153-0154], [0156]) and Examples 6-7 and that antagonists, such as antagonistic antibodies that specifically bind neutrokine-alpha would be able to inhibit each of these activities [0053], [0331]. Applicant also argues that the assertions that neutrokine-alpha stimulates lymphocyte proliferation, differentiation, and survival have been substantiated by post-filing date data. It is noted that Applicant cites MacKay et al. (J Exp Med 190: 1697-1710, 1999), Parry et al. (J Pharmacol Exp Therap 296 :396-404, 2001), Do et al. (J Exp Med 192 : 953-964, 2000), and Huard et al. (J Immunol 167: 6225-6231, 2001). Applicant also submits that by using or routinely modifying assays disclosed in the specification or otherwise known in the art, one of skill in the art, enlightened by the teachings of the specification, can readily determine whether a candidate antibody inhibits lymphocyte proliferation, differentiation, or survival.

Applicant's arguments have been fully considered but are not found to be persuasive. The references made of record (see above and Moore et al. (Science 285: 260-263, 1999), Zhang et al. (J Immunol 166 : 6-10, 2001), Schneider et al. (J Exp Med 189 : 1747-1756, 1999), Thompson et al. (J Exp Med 192:129-135, 2000)) and Examples 6-7 of the specification specifically teach that neutrokine-alpha induces B cell proliferation, differentiation, and survival and displays a clear B cell tropism in both its receptor distribution and biological activity. The specification and the references made of record do not teach that neutrokine-alpha increases/decreases the proliferation, differentiation, or survival of all lymphocyte cells (e.g. T cells). For example, Moore et al. clearly indicate that biotinylated neutrokine-alpha is undetectable on T cells, monocytes, NK cells, and granulocytes and that neutrokine alpha stimulates the proliferation and differentiation of B cells (bottom of pg 260 though pg 261;

Figure 2). Therefore, one skilled in the art would not be able to predict that neutrokine-alpha would be able to increase or decrease the proliferation, differentiation, or survival of any lymphocyte cells, other than B cells. The skilled artisan must resort to trial and error experimentation to determine if neutrokine-alpha increases, decreases, or does not affect the proliferation, differentiation, and survival of T lymphocytes. Such trial and error experimentation is considered undue.

Furthermore, the specification of the instant application and the references cited do not teach inhibiting lymphocyte or B cell proliferation, differentiation, or survival by administering to an individual a therapeutically effective amount of an antagonistic antibody or portion thereof that specifically binds a neutrokine-alpha amino acid sequence. Undue experimentation would be required of the skilled artisan to determine the optimal, quantity, duration, and route of administration of the anti-neutrokine-alpha antibody. There is little or no guidance in the specification indicating what lymphocytes are being specifically targeted by the anti-neutrokine-alpha antibody. For example, are lymphocytes or B cells in the joints being targeted? Cells in the skin? Cells in the thyroid? Administration of the antibody (particularly systemic) would be unpredictable because the skilled artisan would not be able to determine the effect the antibody would have throughout the body. For instance, would the anti-neutrokine-alpha antibody inhibit the proliferation, differentiation, and survival of all lymphocytes, especially B cells, in the body? Although the specification outlines a prophetic example of administration of an anti-neutrokine-alpha antibody [0052-0053], this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Such trial and error experimentation is considered undue. According to MPEP § 2164.06, "the guidance and

ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed".

(ii) Applicant asserts that the specification discloses that neutrokine-alpha antagonists, such as antagonistic antibodies, can be used to treat autoimmune diseases (see for example paragraphs [0050] and [0620]). Applicant reiterates that post filing date data may be used to confirm that the specification was enabling when filed. Applicant states that post filing-date data corroborates the objective enablement of the disclosure by confirming the activity of neutrokine-alpha on lymphocytes; that increased levels of neutrokine-alpha correlate with murine models of autoimmunity as well as with human autoimmune syndromes such as rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome; and that administration of a neutrokine-alpha antagonist, for example soluble forms of neutrokine-alpha receptors such as TACI-Fc or BAFF-Receptor 3, alleviates the symptoms of autoimmune disease in murine models of autoimmunity. It is noted that Applicant cites Gross et al. (Nature 404 : 995-999, 2002), Cheema et al. (Arthritis Rheum 44 : 1313-1319, 2001), Zhang et al. (J Immunol 166 : 6-10, 2001), and Marriette et al (65th Ann Americ Coll Rheumatology Scientific Meeting Nov 2001).

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that post-filing date data indicates neutrokine-alpha is elevated in transgenic mouse models as well as in human syndromes such as rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome. However, the specification does not disclose that neutrokine-alpha is elevated in any autoimmune diseases. Also, neither the specification nor any of the cited references administer an anti-neutrokine-alpha antibody to treat an autoimmune

disease. As discussed above, undue experimentation would be required of the skilled artisan to determine the optimal, quantity, duration, and route of administration of the anti-neutrokine-alpha antibody. Administration of the antibody would be unpredictable because the skilled artisan would not be able to determine the effect the antibody would have throughout the body. The specification outlines a prophetic example of administration of an anti-neutrokine-alpha antibody. However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily treat any autoimmune disease by administration of an anti-neutrokine-alpha antibody. Although the claimed method utilizes routine techniques, the results of the method are unpredictable and complex when combined with the step of administering an anti-neutrokine-alpha antibody.

(iii) Applicant argues that it was known at the time of filing that the vast majority of autoimmune diseases involve either a B cell component and/or a T cell component. Applicant states that at the time of filing, one of skill in the art would have reasonably expected that inhibition of lymphocyte proliferation, differentiation, or survival via administration of

antagonistic anti-neutrokine alpha antibodies would have had an ameliorative effect on autoimmune diseases. Applicant emphasizes that Gross et al. were motivated to treat the symptoms of autoimmune mice with a neutrokine-alpha antagonist based on the knowledge of neutrokine-alpha's biological activities and of elevated levels of neutrokine-alpha in these mice. Applicant also submits that it is not a function of the claims to specifically exclude possible inoperative embodiments, and the presence of inoperative embodiments within the scope of a claim does not preclude enablement of the claim. Applicant cites *Atlas Powder Co. v. E.I. du Pont de Nempurs & Co.*, 750 F2d 1569 at 1576 (Fed. Cir. 1984) and section 2164.08(b) of the M.P.E.P.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the specification teaches that an neutrokine-alpha antibody can be administered to treat a myriad of autoimmune diseases, such as rheumatoid arthritis, dermatitis, multiple sclerosis, Graves' disease, Goodpasture's disease, and asthma, among others (pg 16, [0047]). However, the various autoimmune diseases and disorders disclosed in the specification have different pathophysiologies. For example, rheumatoid arthritis is a chronic, systemic inflammatory disease that is characterized by synovial inflammation and structural damage of articular cartilage and subchondral bone (pg 325-326; Elgert, K. Immunology, understanding the immune system. New York: Wiley-Liss, Inc., 1996). Graves' disease is a disorder of the thyroid gland that is caused by autoantibodies that stimulate thyroid cellular activity by displacing thyroid-stimulating hormone binding (Elgert, K., pg 324, col 2). Asthma is characterized by a constriction of the bronchioles of the lung wherein the tissue surrounding the capillaries of the lung contains mast cells, which, when stimulated by allergen, release histamine, causing

contraction of the smooth muscles (Elgert, K., pg 305, col 2). Undue experimentation would be required of the skilled artisan to administer an anti-neutrokine antibody to individuals with all possible autoimmune disorders and diseases and treat the disorder or disease. One skilled in the art would also not be able to predict from the post-filing date references and the *in vitro* B cell experiments of the instant specification that an anti-neutrokine-alpha antibody would be able to treat all possible autoimmune disorders, such as rheumatoid arthritis and Graves' disease, which have different pathophysiologies. Increased B cell activity is not the only characteristic of autoimmune diseases and neutrokine-alpha is not the only stimulant of B cells, particularly B cells directed to produce antibodies to self antigens as in autoimmune diseases.

Furthermore, although the article cited by Applicant, Gross et al., administers a neutrokine-alpha antagonist to NZBWF1 mice, undue experimentation would still be required by the skilled artisan to deliver an anti-neutrokine-alpha antibody to an individual. Specifically, the fact pattern of the article cited by the Applicant and the claims of the instant rejection are significantly different. For instance, the article discloses administering the neutrokine-alpha antagonist, TACI-Ig fusion protein, which inhibits the development of proteinura and prolongs the survival of the mice. However, the instant claims are to a method of treatment by administration of an anti-neutrokine alpha antibody. At the time the invention was made, the state of the art was such that problems were often encountered in the effort to use antibodies, particularly monoclonal antibodies, as clinical reagents. A few of these problems included: the human immune response to foreign antibodies, low affinity or nonoptimal systemic half-life of antibodies, and difficulty in producing sufficient quantities of antibody for therapy (Moore, Clin. Chem 35: 1849-1853, 1989). Additionally, Ballow et al. (J Am Med Assoc 278(22): 2008-2017,

1997) report that humanized monoclonal antibodies, although less antigenic than chimeric monoclonal antibodies, still elicit antibody production against the idiotypic determinants on the hypervariable region portion of the Ig molecule, shortening serum half-lives (pg 2010, col 3). Ballow et al. also indicate that administration of a chimeric anti-TNF-α monoclonal antibody caused a significant improvement and reduction in acute-phase reactants in patients with rheumatoid arthritis (pg 2011, col 2-3). However, 4-8 after treatment, most patients had disease relapse and retreatment only resulted in temporary improvement (pg 2011, col 3). Ballow et al. state that to achieve continued suppression of the inflammatory response, prolonged or repeated treatment of anti-TNF-α monoclonal antibodies would be necessary (pg 2011, first full ¶). Ballow et al. also conclude that the safety of long-term anti-cytokine therapy remains unknown (pg 2011, first full ¶).

Additionally, the Examiner acknowledges that it is not a function of the claims to specifically exclude possible inoperative embodiments, and the presence of inoperative embodiments within the scope of a claim does not preclude enablement of the claim. However, the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. M.P.E.P. 2164.08(b) states that "claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); *In re Cook,* 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971)". As discussed above in greater detail, undue experimentation would be required of the skilled artisan to treat all possible

autoimmune diseases by administering an anti-neutrokine-alpha antibody. Undue experimentation would also be required by the skilled artisan to target specific lymphocytes in the body and inhibit their proliferation, differentiation, and survival without affecting all lymphocytes.

Due to the large quantity of experimentation necessary to inhibit the proliferation, differentiation, and survival of lymphocytes in an individual by administration of anti-neutrokine-alpha antibody and to treat all possible autoimmune diseases and disorders, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of an anti-neutrokine-alpha antibody in the body (see discussion), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

It is noted that Applicant is encouraged to submit any post-filing date data in the form of a declaration under 37 C.F.R. 1.132.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 85-91, 118-124, and 148-180 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. The term "therapeutically effective amount" in claims 85-91, 118-124, and 148-180 is a relative term which renders the claims indefinite. The term "therapeutically effective amount" is

not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what therapeutic effect is required. (Please note that this issue could be overcome by deleting the term "therapeutically" from the claims.)

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
May 21, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER